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Suzuki Cross-Coupling for the Incorporation of Labeled Methyl Groups onto Aryl Halides. A Synthesis of [^{14}C]Tosyl Chloride and its use in the Synthesis of [^{14}C]L-738,167.

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Summary

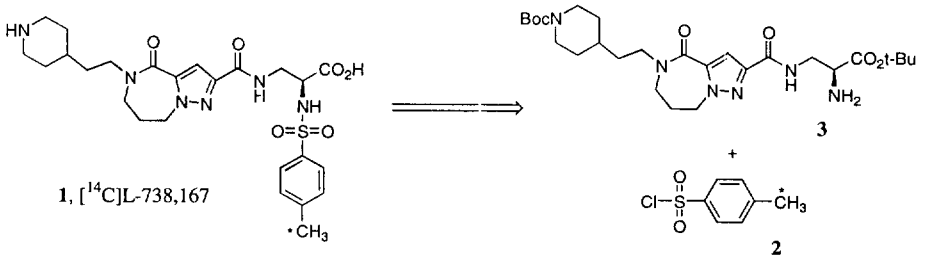
A synthesis of [4-methyl-^{14}C]tosyl chloride (**2**) has been developed which utilizes a Suzuki Cross-Coupling reaction between 4-iodophenylsulfonic acid and a labeled methyl borinate as the key step. This process avoids the poor regioselectivity typically attendant with aromatic sulfonation procedures. We now describe the use of this [^{14}C]tosyl chloride in the synthesis of the orally active fibrinogen receptor antagonist L-738,167 (**1**).

Keywords: Suzuki Cross-Coupling, Fibrinogen Receptor Antagonist, L-738,167, [^{14}C]tosyl chloride, synthesis.

Introduction

Orally active fibrinogen receptor antagonists are a potentially valuable class of compounds for the prevention of thrombolytic disorders associated with platelet aggregation.[1] In the course of developing one such compound at Merck, L-738,167 (**1**), synthesis of a carbon-14 labeled analog was required.[2] Retrosynthetically, our plan was to take advantage of the in-house availability of amine **3** for late stage incorporation of the label with [^{14}C]tosyl chloride (**2**) (Scheme 1).

Scheme 1



1, [^{14}C]L-738,167

3

2

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In the course of developing the route depicted in Scheme 1, we found that commercially available [4-methyl-^{14}C]tosyl chloride may contain up to 50% of the 2-methyl isomer. This is due to the method of preparation - sulfonation of [methyl-^{14}C]toluene - and subsequent difficulty in separating the regioisomers. Since the purification of either **2** or **1** contaminated with regioisomer was an exceedingly difficult task, we sought a synthesis of **2** which would afford only the desired 4-methyl isomer. We reasoned that cross-coupling of a 4-halobenzenesulfonic acid with an organometallic reagent capable of transferring a methyl group would be an attractive solution (Figure 1). Although the transition metal catalyzed cross-coupling of labeled methyl iodide with various organometallics has been well exploited,[3] reports of the reverse process, using a labeled methyl-organometallic, are relatively rare and inefficient.[4] Aside from providing a source of isomerically pure **2**, we were interested in the possibility of such a cross-coupling to provide general means of installing labeled methyl groups ($H_3{}^{14}C$-, $H_3{}^{13}C$-, ^2H_3C-) in cases where a halogen or triflate substituted precursor is available. To this end, we felt the Suzuki reaction, which utilizes an organoboron reagent as the organometallic partner, would be most suitable (Figure 2).

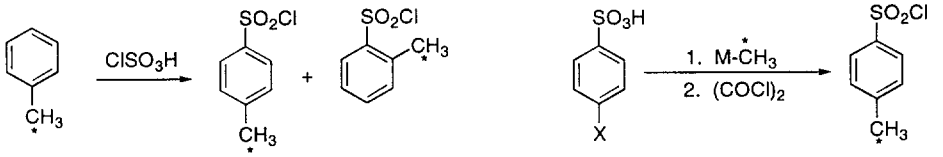


Figure 1. Sulfonation vs. Cross-Coupling

The Suzuki reaction has become a tremendously popular means of carbon-carbon bond formation due to generally high yields, wide substrate tolerability, ease of operation, mild reaction conditions, and ready availability of the requisite boron reagents.[5] Methylation of organic halides/triflates via the Suzuki reaction has been carried out using methyl boronic acid

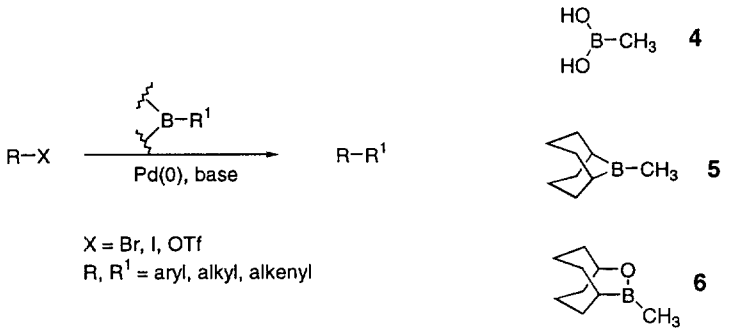


Figure 2. Suzuki Reaction and Established Suzuki Methylation Reagents

(**4**),[6] 9-methyl-9-borabicyclo[3.3.1]nonane (**5**),[5] and 10-methyl-9-oxa-10-borabicyclo[3.3.2]-decane (**6**).[7] Of these, **4** and **6** were most attractive as labeling reagents because of their air stability.

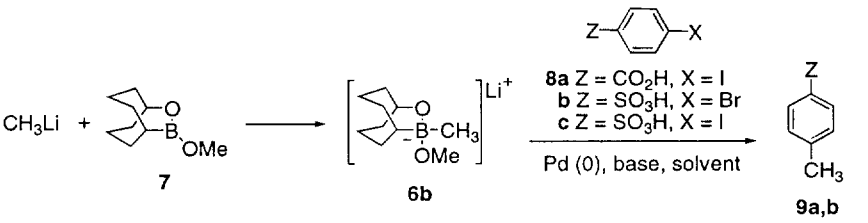
Results and Discussion

We began our investigation using methyl boronic acid (**4**) as the methyl donor due to its ease of handling and preparation. Unfortunately, all cross-coupling attempts with this reagent failed to give any conversion. We then turned our attention to the air stable oxa-boranes pioneered by Soderquist.[8] Oxa-borinate **7** was easily prepared from 9-BBN-H by treatment with methanol followed by selective oxidation with anhydrous trimethylamine N-oxide.[8,9] We anticipated that reaction of **7** with an organolithium reagent would afford the borinate ester-LiOMe complex **6b** which could be used in situ for the cross-coupling (Table 1).[10] This was indeed the case, as *p*-iodobenzenesulfonic acid (**8c**) underwent 80% conversion to *p*-toluenesulfonic acid under Suzuki conditions (Table 1, entry 6). The aryl bromide **8b** did not undergo appreciable cross-coupling under identical conditions. Since any remaining aryl halide would complicate direct use of the coupled product, we attempted to optimize the reaction for complete conversion. Optimization with respect to base was carried out using 4-iodobenzoic acid (**8a**) with the finding that additional base (above the 1 eq of methoxide initially present) is necessary and aqueous K_3PO_4 and $Ba(OH)_2$ are more effective than NaOH (Table 1, entries 1-4).

After carrying out several cross-couplings using $Ba(OH)_2 \cdot 8H_2O$ as the base of choice, we found that the cross-coupling was highly variable with respect to the methylborinate batch. This led us to believe that the methyl lithium/boronic ester ratio was crucial for an effective methyl transfer reagent. Using either a deliberate undercharge or overcharge of **7** (Table 1, entry 7 vs. 8), we confirmed that an excess of methyl lithium relative to **7** is necessary for optimum conversion. All subsequent methylations were performed with an excess of MeLi (0.05-0.1 eq) resulting in a reliably clean and rapid conversion. No attempts to optimize the reaction with respect to catalyst were made.

With a reliable cross-coupling procedure in hand we were able to prepare [4-methyl-^{14}C]tosyl chloride in 54% overall yield based on [^{14}C]MeI (Scheme 2). An excess of the [^{14}C]methylborinate **6b** was employed to ensure complete consumption of the starting aryl iodide. The crude sulfonate salt obtained from the cross-coupling reaction was directly converted to the sulfonyl chloride in quantitative yield by treatment with oxalyl chloride and catalytic DMF. Although the entire sequence requires several steps, it is a two-pot process with no purification steps and consistently provided crude [4-methyl-^{14}C]tosyl chloride suitable for direct use (>97% radiochemical purity by HPLC).

Table 1. Cross-coupling of methyl-oxa-borane **6b** with aryl halides.[a]



entry	substrate	MeLi/7	base[b]	temp/time	% convn[c]
1	**8a**	1	none	rt, 12h	<5
2	**8a**	1	3N NaOH	rt, 12h	16
3	**8a**	1	3M K_3PO_4	rt, 12h	53
4	**8a**	1	$Ba(OH)_2 \cdot 8H_2O$	rt, 12h	57
5	**8b**	1	3N NaOH	50 °C, 2h	<5
6	**8c**	1	3N NaOH	50 °C, 2h	80
7	**8c**	0.9	$Ba(OH)_2 \cdot 8H_2O$	rt, 0.5h	69
8	**8c**	1.1	$Ba(OH)_2 \cdot 8H_2O$	rt, 0.5h	100

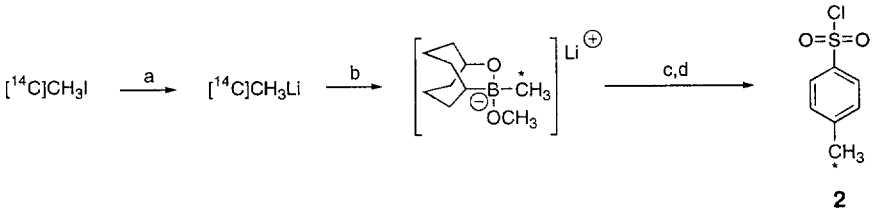
[a] All reactions were run in DMF-THF (1:1) with $PdCl_2(PhCN)_2$ (5 mol%) and Ph_3As (10 mol%).
[b] 3-3.5 eq of base were used except for reactions with $Ba(OH)_2 \cdot 8H_2O$ in which 2 eq were used.
[c] Percent conversion is defined as [area% coupled product/ area% coupled product + area% aryl halide]100, as determined by HPLC with UV detection at 254 nm.

[^{14}C]TsCl thus prepared was employed in the straightforward synthesis of the oral fibrinogen receptor antagonist L-738,167 (**1**) (Scheme 3). Sulfonamide formation and deprotection provided the triflate salt of **1** in 41% overall radiochemical yield after purification. The salt was converted to the free base (zwitterionic form) on a Dowex 80X-200 acidic ion-exchange column and crystallized twice from water to provide **1** (3.8 mCi, 14% overall radiochemical yield from [^{14}C]MeI) with a radiochemical purity of 98.5% by HPLC.

Conclusion

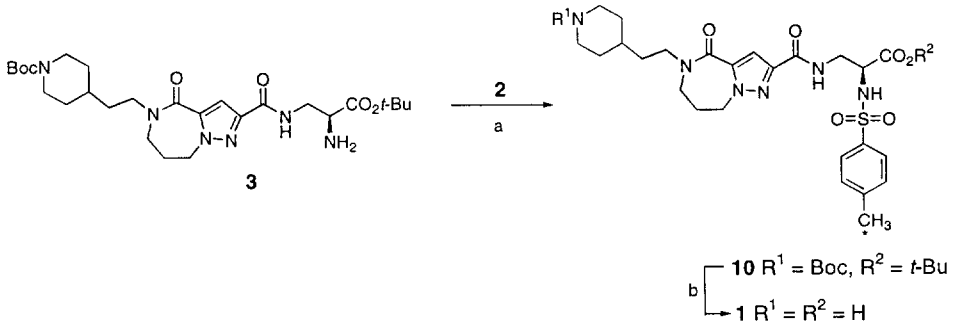
In conclusion, we have found that the Suzuki reaction can serve as a rapid and efficient means of installing labeled methyl groups onto aryl halides. The functional group tolerance and compatibility with aqueous solvent should allow for the use of Suzuki methylation in the labeling of a wide variety of compounds with minimal use of protecting groups.

Scheme 2[a]



[a] Reagents and conditions: (a) butyllithium, hexane, 0 °C (ref. 11); (b) **7**, THF, -78 °C; (c) 4-iodobenzenesulfonic acid, $Pd(PhCN)_2Cl_2$, Ph_3As, DMF, 60 °C; (d) oxalylchloride, DMF, CH_2Cl_2, rt.

Scheme 3[a]



[a] Reagents and conditions: (a) **2**, Et_3N, CH_2Cl_2; (b) TFA, CH_2Cl_2.

Experimental

Radioactivity measurements were carried out using a Packard Tri-carb 1000 TR liquid scintillation spectrometer and Scintiverse I™ as scintillant. Analytical HPLC measurements were conducted using a DuPont Zorbax SB-C8 column (4.6 x 250 mm) or a Phenomenex Primesphere C-18 column (4.6 x 250 mm), IBM UV detector, Packard Radiomatic™ 500TR flow scintillation analyzer with Scintiverse I™ scintillation cocktail, and Thermo Separation Products P4000 pump and controller. Preparative scale HPLC was accomplished with a DuPont Zorbax Rx-C8 column (21 x 250mm), Rainin pumps controlled by a Macintosh computer, and Beckman Model 153 UV detector with fixed wavelength at 254 nm.

^{1}HNMR spectra were measured at 400 MHz on a Varian Unity-400 spectrometer. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane (TMS).

9-BBN-H,[12] B-methoxy-9-BBN,[9] B-methoxy-oxa-9-BBN (**7**),[8] and $PdCl_2(PhCN)_2$,[13] were prepared according to literature methods. Amine **3** was obtained in-house according to the published procedure.[2] 4-Iodobenzenesulfonic acid was prepared by the aqueous hydrolysis of

pipsyl chloride (Aldrich Chemical Co.). All other reagents were obtained from the Aldrich Chemical Company and used as is. Commercial anhydrous THF was dried over 4A molecular sieves before use. All reactions were carried out under a nitrogen atmosphere.

The identities of labeled intermediates and final product were established by co-elution, via HPLC, of the labeled substance with authentic standards obtained from either Aldrich Chemical Co. (Milwaukee, WI) or in-house sources. In the case of the final product **1**, a ^{1}H NMR spectrum was obtained which was found to be identical to that of unlabeled reference.[1]

[4-methyl-^{14}C]tosyl chloride (2)

[^{14}C]MeLi was prepared by an adaptation of the literature route.[11] A 4 mL closed-end glass tube with 14/20 ground-glass joint, and magnetic stir bar, was connected to a gas transfer manifold and flame-dried under nitrogen. The tube was then charged with dry hexane (100μL) and n-BuLi (182 μL of a 2.5 M solution in hexane, 0.456 mmol). The solution was frozen with liquid nitrogen and [^{14}C]MeI (26 mCi, 57 mCi/mmol, 0.456 mmol) admitted via a break seal vessel attached to the manifold. The mixture was thawed with a dry ice-acetone bath and then allowed to warm to rt at which point a white precipitate of [^{14}C]MeLi formed. After stirring for 20 min. the solution was cooled to -20 °C and centrifuged. The supernatant was removed and the solid pellet washed with cold, dry, hexane (2 x 200 μL). The solid was finally dissolved in 0.8 mL dry THF affording a cloudy solution of [^{14}C]MeLi (17.4 mCi, 67% radiochemical yield, >98% radiochemical purity).[14]

The above solution of [^{14}C]MeLi was cooled to -78 °C with an acetone-dry ice bath and B-methoxy-oxo-9BBN (**7**) added (46 μL, 0.274 mmol). The cooling bath was removed and the solution stirred at room temperature for 1 h. At this time, in a separate flask, was placed 4-iodobenzenesulfonic acid (64 mg, 0.224 mmol), $Ba(OH)_2$•$8H_2O$ (143 mg, 0.40 mmol), $PdCl_2(PhCN)_2$ (3 mg, 3.5 mol%), and Ph_3As (5 mg, 7 mol%). The solids were suspended in DMF (1.5 mL) and warmed to 60 °C. The THF solution of [^{14}C]borinate **6b**, described above, was then added via syringe. The reaction became dark and was deemed complete at 15 min by HPLC analysis (Zorbax Rx-C8 column, 4.6 x 250 mm, 5% acetonitrile:H_2O (0.1% TFA) to 95% acetonitrile, 20 min linear gradient, 1 mL/min, 220 nm, *p*-toluenesulfonic acid t_R = 7.7 min, *p*-iodobenzenesulfonic acid t_R = 10.2 min). The mixture was diluted with water (15 mL), washed with ethyl acetate (3 x 3 mL), and filtered. The aqueous solution of sulfonate salt was evaporated to a thick syrup and suspended in CH_2Cl_2 (15 mL). DMF (10 μL) was added, the solution was cooled with an ice-bath, and an excess of oxalyl chloride (500 μL) was added. The mixture was stirred at room temperature for 0.5 h at which time radio-HPLC indicated [^{14}C]tosyl chloride as the sole component (Zorbax Rx-C8 column, same conditions as above, *p*-toluenesulfonyl

chloride t_R = 19.6 min). The mixture was carefully quenched with saturated $NaHCO_3$ till bubbling ceased and was then washed with saturated $NaHCO_3$ (2 x 5 mL) followed by water (1 x 5 mL), and brine (1 x 5 mL). The brown-orange solution was dried over $MgSO_4$ and filtered to provide crude [^{14}C]TsCl (14 mCi, 54 % radiochemical yield from [^{14}C]MeI) which was used without further manipulation.

t-Butyl-2-(*S*)-[4-[^{14}C]methyl-benzenesulfonylamino]-3-[[[5,6,7,8-tetrahydro-4-oxo-5-[2-(N-Boc-piperidin-4-yl)ethyl]-4-H-pyrazolo[1,5-a][1,4]diazepin-2-yl]carbonyl]amino]-propionic acid (12)

The above formed solution of [^{14}C]tosyl chloride (14 mCi, 0.27 mmol) in CH_2Cl_2 was adjusted to a volume of 12 mL and amine **3** (149 mg, 0.271 mmol) was added followed by triethylamine (220 mL, 3 mmol). The mixture was stirred at room temperature for 1.5 h at which point HPLC analysis indicated that all [^{14}C]TsCl had been consumed. The solution was then washed with 10% $KHSO_4$ (2 x 4 mL), water (1 x 4 mL), saturated $NaHCO_3$ (1 x 4 mL), and brine (2 x 3 mL). The solution was dried over $MgSO_4$, filtered, and solvent removed. The residue was purified by silica gel chromatography using ethyl acetate as eluant, to afford 7.4 mCi (135 mg) of product with a radiochemical purity of 95% by HPLC analysis (Zorbax Rx-C8 column, 4.6 x 250 mm, 30% acetonitrile:H_2O (0.1% TFA) to 95% acetonitrile, 20 min linear gradient, 1 mL/min, 220 nm, **12** t_R = 17.2 min).

2-(*S*)-[4-[^{14}C]methyl-benzenesulfonylamino]-3-[[[5,6,7,8-tetrahydro-4-oxo-5-[2-(piperidin-4-yl)ethyl]-4-H-pyrazolo[1,5-a][1,4]diazepin-2-yl]carbonyl]amino]-propionic acid (1)

Protected intermediate **12** (135 mg, 7.4 mCi) was taken into CH_2Cl_2 (5 mL) and cooled to 0 °C. The solution was treated with TFA (2.5 mL) and allowed to warm to room temperature. After 3 h the solvent was removed on a rotary evaporator and the residue taken into 5 mL of acetonitrile/water (1:1). The solution was filtered and applied to a preparative HPLC column (2 injections). The most pure fractions were combined and evaporated to yield 6.2 mCi of **1** as the triflate salt. The salt was converted to the zwitterionic form by eluting through a Dowex 80X-200 acidic ion exchange column with water followed by $NH_4OH/H_2O/CH_3CN$ (2:1:1). Product containing fractions were evaporated, taken into water (9 mL), and filtered. The volume was reduced to 1.5 mL and 75 mg of unlabeled L-738,167 added. Dissolution was effected with warming and on cooling the product crystallized. After aging 0.5 h at 10 °C the solid product was collected by filtration and washed with cold water (1 mL). The crystallization was repeated and the resulting solid dried *in vacuo* to give 94 mg (3.8 mCi) of the title compound **1** with a radiochemical purity of 98.6% by HPLC (Phenomenex Primesphere-C18 column, 4.6 x 250 mm, 15% acetonitrile (0.1% TFA):H_2O (0.1% TFA) to 60% acetonitrile (0.1% TFA), 20 min linear

gradient, 1 mL/min, 230 nm, **1** t_R = 15.8 min). ^{1}H NMR (DMSO-d_6) δ 8.24 (dd, 1H, *J* = 6.82, 3.2 Hz), 7.63 (d, 2H, *J* = 8.2 Hz), 7.32 (d, 2H, *J* = 8.2 Hz), 6.86 (s, 1H), 4.36 (t, 2H, *J* = 6.91 Hz), 3.67 (ddd, 1H, *J* = 12.57, 6.3, 5.9 Hz), 3.46 (t, br, 2H, *J* = 6.82 Hz), 3.36-2.98 (m, br, 8H), 2.77 (dt, 2H, *J* = 12.57, 2.63 Hz), 2.33 (s, 3H), 2.16 (t, 2H, *J* = 6.43 Hz), 1.80 (d, br, 2H, *J* = 12.7 Hz), 1.54-1.42 (m, br, 3H), 1.30-1.18 (m, br, 2H).

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